FDA Approves AZEDRA Specified Use in Pheochromocytomas/Paragangliomas

The U.S. Food and Drug Administration (FDA) announced on July 30 its approval of a ^{131}I-iobenguane injection agent (AZEDRA; Progenics Pharmaceuticals, Inc., New York, NY) for intravenous use for treatment of adult and pediatric patients (≥12 years old) with iobenguane scan–positive, unresectable, locally advanced, or metastatic pheochromocytomas or paragangliomas who require systemic anticancer therapy. This is the first FDA-approved drug for this use.

"Many patients with these ultra-rare cancers can be treated with surgery or local therapies, but there are no effective systemic treatments for patients who experience tumor-related symptoms such as high blood pressure," said Richard Pazdur, MD, director of the FDA Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA Center for Drug Evaluation and Research. "Patients will now have an approved therapy that has been shown to decrease the need for blood pressure medication and reduce tumor size in some patients."

AZEDRA is a high-specific-activity ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) agent made up almost entirely of labeled MIBG molecules, allowing for lower mass doses of MIBG to be administered. AZEDRA was approved through an FDA Priority Review mechanism, based on a Special Protocol Assessment (SPA; 2009) of the results of a pivotal study of treatment of iobenguane scan–positive, unresectable, locally advanced, or metastatic pheochromocytomas and paragangliomas. The agent received an FDA Fast-Track designation and Orphan Drug status in 2006, as well as a breakthrough therapy designation in 2015. The European Medicines Agency granted AZEDRA Orphan Drug status in neuroblastoma in 2008.

FDA approval was based in part on updated data from a phase 2 open-label, multicenter trial conducted under an SPA. The original study included 68 patients with pheochromocytomas or paragangliomas and assessed the number of patients who experienced a ≥50% reduction of all antihypertensive medications lasting for at least 6 months. This endpoint was supported by a secondary endpoint, overall tumor response measured by the Response Evaluation Criteria in Solid Tumors. The study met the primary endpoint, with 17 (25%) evaluable patients experiencing a 50% or greater reduction of all antihypertensive medication for at least 6 months. Overall tumor response was achieved in 15 (22%) patients. Of these 15 patients, 53% experienced durable tumor responses lasting 6 months or longer. Ninety-two percent of patients treated with at least 1 therapeutic dose of AZEDRA achieved a confirmed partial response or stable disease by 12 months. Updated data on the study are currently being reviewed for publication in an upcoming issue of *The Journal of Nuclear Medicine.*

AZEDRA was also shown to be safe and generally well tolerated. The most common severe (Grade 3–4) adverse reactions (≥10%) were lymphopenia (78%), neutropenia (59%), thrombocytopenia (50%), fatigue (26%), anemia (24%), decrease in blood clotting time (18%), nausea (16%), dizziness (13%), hypertension (11%), and vomiting (10%). Twelve percent of patients discontinued treatment as a result of adverse reactions. The agent carries radiation exposure warnings similar to those of other radioactive therapeutic agents.

"Azedra has shown the potential to significantly improve outcomes in patients with MIBG-avid neuroendocrine tumors," said Steven Larson, MD, Donna and Benjamin M. Rosen Chair in Radiology, at Memorial Sloan Kettering Center (New York, NY). "This is the first regimen to demonstrate robust clinical benefit in patients with iobenguane scan–positive, unresectable, locally advanced, or metastatic pheochromocytoma or paraganglioma and brings with it the hope for prolonged survival with manageable toxicity. We thank all those involved in this important milestone for the neuroendocrine and nuclear medicine communities, which provides hope for patients with limited treatment options."

Emily Collins, president of the Pheo Para Alliance, a patient advocacy group, echoed this assessment: "The FDA's approval of AZEDRA is welcome news to patients with pheochromocytoma and paraganglioma, who have an extremely limited number of treatment options available to them. The drug's Fast Track status and Breakthrough Therapy designation by the FDA underscore the dire need for the development and expeditious review of diagnostic and therapeutic agents for pheo/para that, generally, don't get adequate prioritization despite the growing prevalence of these and other neuroendocrine tumor cancers globally."

AZEDRA is available as a frozen drug product for preparation or in a ready-to-use vial from a commercial radiopharmacy. The agent is being evaluated for utility in other iobenguane scan–positive cancer indications.